IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Daniel C. Sigg et al.	Examiner:	J. Reidel
Serial No.	10/766,792	Group Art:	3762
Filing Date:	January 28, 2004	Docket No.:	P11213.00
Title:	ANTITHROMBOGENIC MEDICAL DEVICE		

DECLARATION UNDER 37 C.F.R. § 1.131 ANTEDATING A REFERENCE

I hereby declare the following:

1) I am currently and correctly named as an inventor in the pending patent application entitled "Antithrombogenic Medical Device", U.S. patent application serial number 10/766,792.

2) The invention disclosed within the above-referenced patent application was conceived of by me and the other named inventors before September 30, 2003.

3) An Invention Disclosure Form was completed that described the invention and was submitted to the Medtronic, Inc. legal department for consideration before September 30, 2003 (a copy of said form is attached hereto).

4) My inventor's log along with a report entitled "NO Releasing Polymer Prevent Thrombus Formation" establish reduction to practice the present invention before September 30, 2003.

5) All of the work related to reduction of practice of the present invention were performed in the United States.

6) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 4-3-06

Daniel C. Sigg

NonGLP

NO releasing polymer to prevent thrombus formation
Study No.: 0002S0001
Acct. No.: T0050/B4533

Study Sponsor: Daniel Sigg — Date [redacted]

Animal Care and Use Committee — Date [redacted]

Study Director: Maria Benavides — Date [redacted]

Physiological Research Laboratories
Division of Medtronic, Inc.
1385 115th Avenue N.W.
Minneapolis, MN 55448

Initial Study Team
Maria Benavides, Study Director
Jon Urban, Back-up Study Director
Kyle Hardel, Ericka Stauffer, and Shellee Lamb, Animal Care
Nancy Rakow, Veterinarian
Phillip Faulkner, Veterinarian
Linnea Lentz, Veterinarian
Gail Snyder, Surgery Tech
LeAnn Alfson, Surgery Tech
Sandra Wyffels, Clin-Lab
Rebbeca Rose, Pathologist
Mark Petersen, Pathologist
Louanne Cheever, Path. Assistant
Robin Miller, Path. Assistant
Daniel Sigg, Study Sponsor

TABLE OF CONTENTS

PROTOCOL PROFILE

Study Information	Study Title	NO releasing polymer to prevent thrombus formation
	Short Study Title	NO releasing polymer
	Study (AR) Number	0002S0001
	Account Number	T0050/B4533
	Study Sponsor	Daniel Sigg
	Study Director	Maria Benavides
	Backup Study Director	Jon Urban
	GLP Compliance	N/A
Animal Information	Species	Pig
	Number	7 (5 animals for the study, 1 animal for methods development, 1 animal for back up)
	Weight Range	40-60 kg
	Duration	1 Day
	Sex	Male or Female
	Animal Training	NA
Surgery	Surgery Type	Arteriotomy
	Test materials/devices	NO Releasing Polyurethane film Catheter
	Control materials/devices	Polyurethane film Catheter
Surgery Equipment	Sponsor to supply	NA
	PRL to supply	Equipment necessary to perform arteriotomy
Monitor Equipment	Sponsor to supply	Test and control materials/devices
	PRL to supply	NA
Termination Equipment	Sponsor to supply	NA
	PRL to supply	Camera

Protocol Schedule

Procedure	Time Point (week)	Premedication/ Anesthesia	Imaging	Clinical Laboratory	Data Acquisition
Pre-Implant	-1	Antibiotics will be given prior to surgery. Analgesics and Verapamil and Dantrium may be given as prescribed by staff veterinarian.	None	Pre-operative blood work: CBC, platelet, count, ACT	None
Implant	0	Acepromazine, and Telazol, and maintained on isoflurane at the discretion of the staff veterinarian.	None	None	None
Anesthetized Term	1 day post implant	Acepromazine, and Telazol, maintained on isoflurane and Pentobarbital IP at the discretion of the staff veterinarian.	None	Prior to heparinization, CBC, platelet, count, ACT	None

Pathology	
Requirements	Gross pathology, Low vacuum SEM, and routine histology

I. BACKGROUND & PURPOSE

A. Purpose

To evaluate the use of Nitric-oxide releasing polymers to reduce the activation of coagulation in vivo.

B. Background

Difficulties in extracting pacing and defibrillator leads and other chronically implanted devices are an ongoing clinical issue, and occasionally require an invasive approach with special tools (laser) or even surgery. Most of difficulties associated with lead extraction are due to pronounced fibrosis/encapsulation. Fibrosis/encapsulation is due to the foreign body tissue response to the surface of the implanted materials, which leads to platelet (thrombocyte) activation, adhesion, thrombus formation, and ultimately fibrosis. Nitric oxide (NO) is an important signaling molecule, and is involved in many physiological processes. Important for the present study is the fact that NO prevents platelet activation and adhesion (1). A white thrombus is formed by fibrin and platelets, and may subsequently develop into a red thrombus (erythrocytes and other blood cells). NO delivery to the surface of implanted materials seems to be a logical approach to prevent thrombus formation and subsequent fibrosis/encapsulation. And indeed, it has been shown that NO releasing polymer coated tubing implanted in arteries was associated with significantly reduced thrombocyte adhesion and thrombus formation in vivo (2). However, most of these approaches use NO precursors loaded into the polymer coating film, and therefore, eventually lead to an exhaustion of NO release (within days). Nitric-oxide releasing polymers reduce the activation of coagulation in vivo, and therefore, at least conceptually, may lead to long-term NO-release (weeks-months-years).

C. Study Design

Each animal will receive a total of 4 devices two treatment and two control devices.

Treatment group will receive the test devices as follows: Catheter coated with NO-releasing polyurethane film (about 100 micron). 2 treatment devices will be implanted per animal, 1 in femoral artery (right or left), and 1 in carotic artery (right or left). A randomization table will determine right or left implantation.

The control group will receive the Control devices as follows: 2 control devices (Catheter coated with polyurethane film (control, not NO-releasing)) will be implanted: 1 in the femoral artery and 1 in the carotid artery.

II. STUDY OBJECTIVE (S)

A. Test coagulation on the surface of an implanted device in vivo

B. To determine if NO releasing polymer films are associated with reduced thrombocyte adhesion and thrombus (white and red) formation via SEM analysis

C. To determine the effects of Nitric Oxide on coagulation via pathohistological (gross pathology) analysis.

D. To determine if any acute adverse histopathological effects are observed.

III. TEST ARTICLE (S), CONTROL ARTICLE (S), AND TEST SYSTEM (S)

A. Test Article(s)

- NO Releasing Polyurethane film Catheter

B. Control Article(s)

- Polyurethane film Catheter (Catheter coated with 100 um polyurethane film)

C. Test System(s)

1. Species: Pig
2. Number: 7 (5 animals for the study, 1 animal for methods development, 1 animal for back up)
3. Weight Range: 40 - 60 Kilograms
4. Sex: Male or Female
5. Age: Adult
6. Source of Supply: Genetipors

IV. PRE-IMPLANT

A. Animal Preparation

1. Medications (At the discretion of the Staff Veterinarian)
   a) Pre-operative antibiotics will be started prior to surgery.
   b) Pre-operative analgesics may be started prior to surgery.
   c) Verapamil and Dantrium may be may be given as prescribed by staff veterinarian the morning of surgery prior to surgery.
   d) The animal will be heparinized.
   e) Steroid medications will NOT be given unless deemed critical to the health of the animal, as determined by a veterinarian, with the approval of the study sponsor and study director.
2. Other
   a) The animal will be fasted prior to surgery.
   b) The animal will be bathed prior to surgery.

B. Clinical Laboratory

1. Complete blood count (CBC), platelet count, and ACT, testing will be performed prior to implant.

C. Data Collection

1. None.

V. SURGERY

A. Schedule Considerations

1. None.

B. Equipment

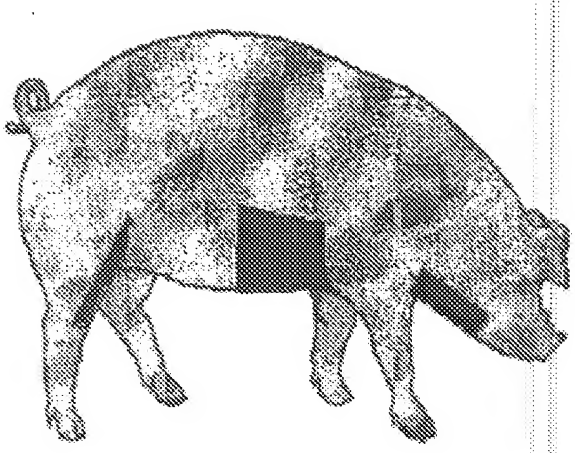
1. Study Sponsor to Supply:
   - None
2. PRL to Supply:
   - Equipment necessary to perform venotomy and arteriotomy

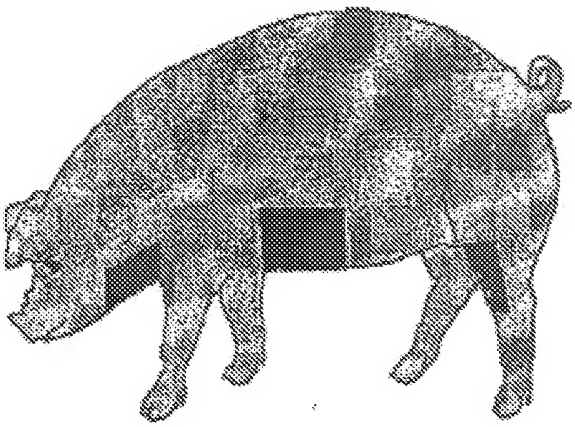
C. Animal Preparation

1. Medications
   a) Antibiotics will be given prior to surgery.
   b) Analgesics may be given as prescribed by staff veterinarian.
   c) Verapamil (SR) (360 mg, SID) and Dantrium may be given as prescribed by staff veterinarian the morning of surgery. Telazol (3 mg/kg) /Acepromazine (1 mg) prior to intubation, maintenance on isoflurane
   d) The animal will be heparinized.
   e) Steroid medications will NOT be given unless deemed critical to the health of the animal, as determined by a veterinarian, with the approval of the study sponsor and study director.
2. Sedation and/or Anesthesia
   a) An analgesic will be given to the animal prior to sedation. Animals will be induced with Acepromazine, Telazol and maintained on isoflurane.
3. Other

   None.

Figure 1. Area to be prepped and clipped





D. Surgical Procedure

1. All implanted devices will be sterilized prior to surgery.
2. Surgical Access for Carotid Artery and catheter placement: the carotid artery will be accessed via percutaneous entry per a modified Seldinger technique. At the discretion of the veterinary surgeon, arterial access may also be performed via subcutaneous cutdown. A minimal incision may be made to isolate the carotid artery.

```
ERROR: ioerror
OFFENDING COMMAND: image

STACK:

-savelevel-
```

Specimen Number: 040464
on Page No. _____
Study No.: S1086
Acct. No.: B4533
Species: Porcine
Animal No. 328560
Necropsy Date: [redacted]
GLP: _____ NON-GLP X

04-409
1. Polymer 9
2. Najen CP-11
3. Polymer 7
4. Najen CP-7

Specimen Number: 040461
Study No.: S1086
Acct. No.: B4533
Species: Porcine
Animal No. 328574
Necropsy Date: [redacted]
GLP: _____ NON-GLP X

04-410
1. Najen CP-4
2. Polymer 4 button
3. Najen CP-5
4. Polymer 3 button

Specimen Number: 040459
Study No.: S1086
Acct. No.: B4533
Species: Porcine
Animal No. 328582
Necropsy Date: [redacted]
GLP: _____ NON-GLP X

04-411
1. Polymer 8
2. Najen CP 12
3. Polymer 10
4. Najen CP 10

No histo done on this page

To Page No. _____

Witnessed & Understood by me, N/A | Date N/A | Invented by [redacted] | Recorded by [redacted] | Date [redacted]

Page No.
men Number: 040448
No.: S1067
No.: P4177
es: canine
al No. 001123
psy. Date: [redacted]
NON-GLP X
trimmed by L Phillips
[redacted]

04-401
402 A Right, Superior, Slice 1
B. ↓ " Slice 2
C ↓ Inferior, Slice
d. Left, Superior, Slice 1
e. Superior, Slice 2
F. Inferior, Slice 1
g Inferior, Slice 2

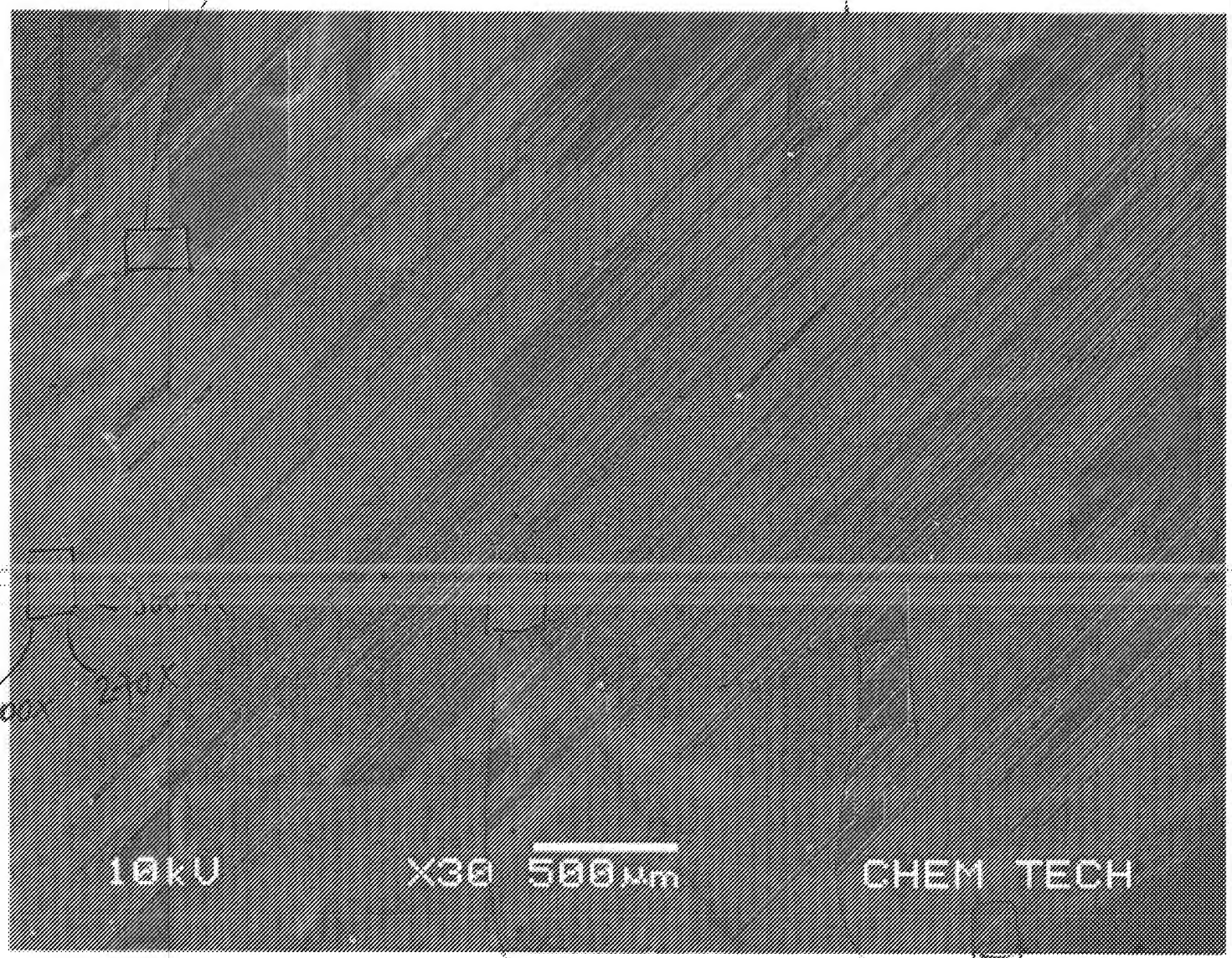
ten Number: 040455
No.: S1086
lo.: B4532
e: P.O
LNo. 328583
sy. Date: [redacted]
NON-GLP X
trimmed by K. Wika
[redacted]

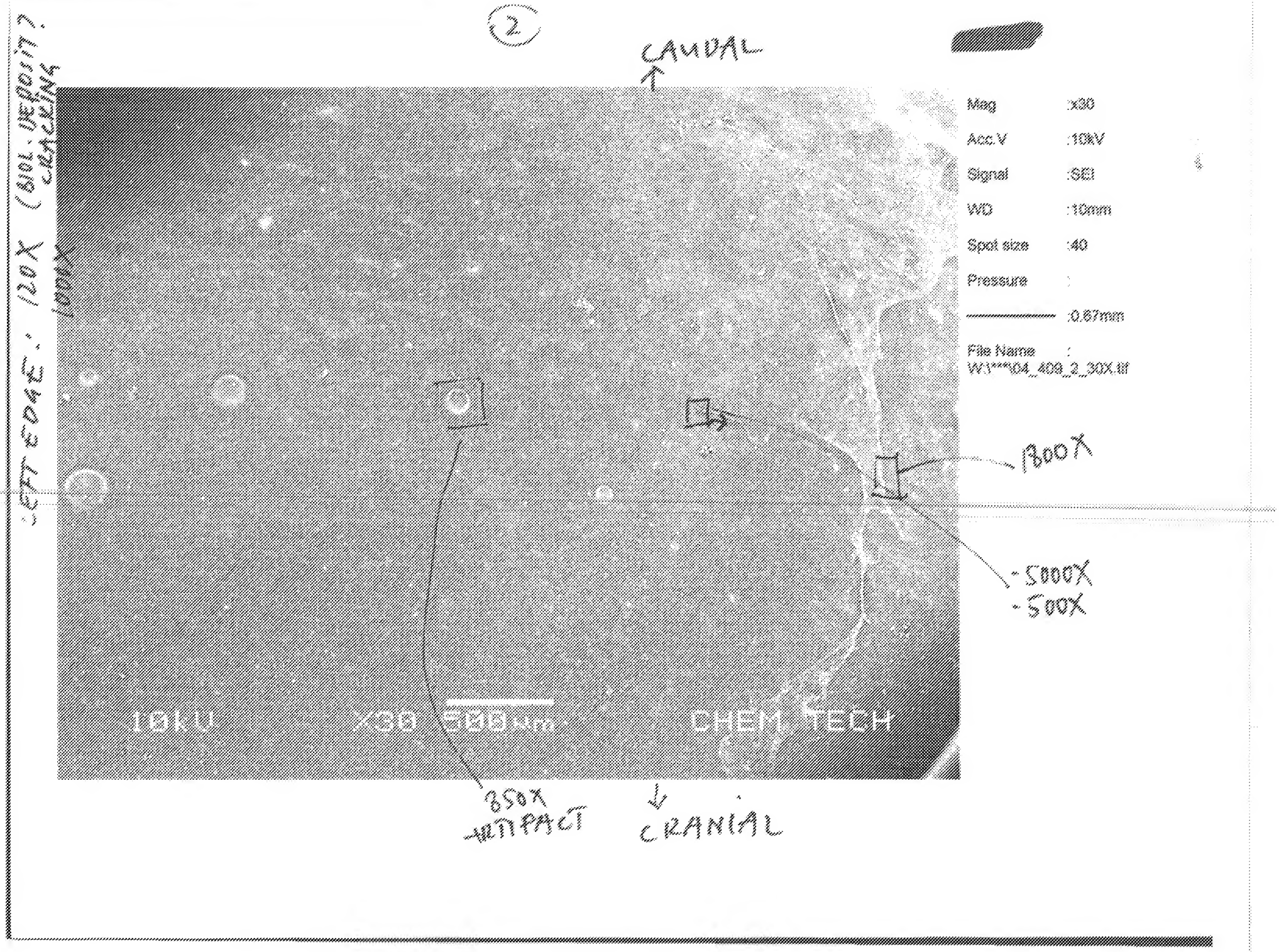
04-403 A ① Nojen-CP-1
② Nojen-CP-3
③ Polymer 1
④ Polymer 2

No histo done

To Page No.

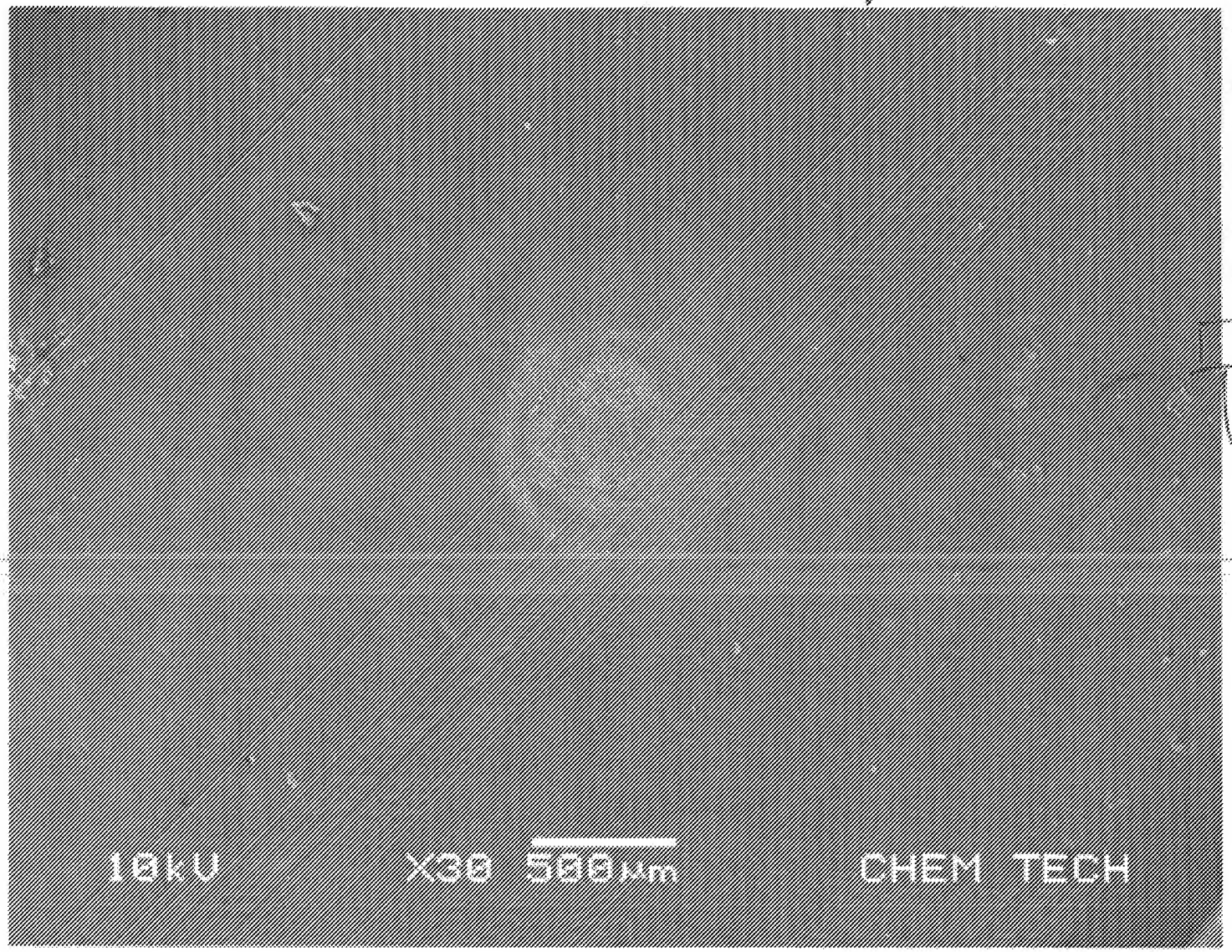
essed & Understood by me, | Date | Invented by | Date
A.A | N/A | Recorded by AT | [redacted]


500X
1
CAUDAL
12/21/2004
Mag :x30
Acc.V :10kV
Signal :SEI
WD :11mm
Spot size :40
Pressure :
:0.67mm
File Name :
W:***04_409_1_30X.tif
170X
1200X
2000
9000X
500X
10kU
X30 500µm
CHEM TECH
500X_2
CRANIAL
not photographed but looked like similar lesions

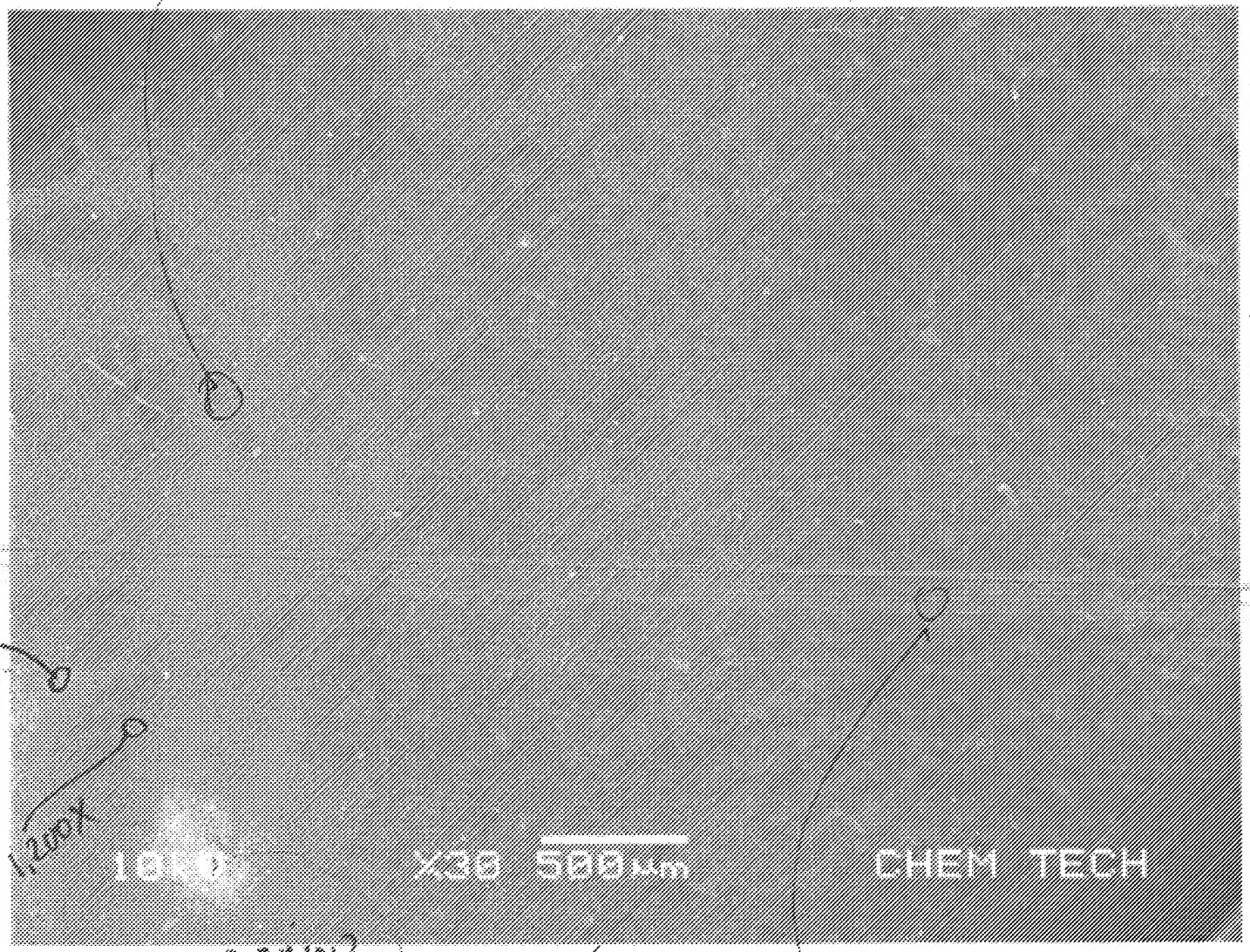

2
CAUDAL
Mag :x30
Acc.V :10kV
Signal :SEI
WD :10mm
Spot size :40
Pressure :
:0.67mm
File Name :
W1***04_409_2_30X.tif
LEFT EDGE: 120X (COL. REPORT: CRACKING 100X)
800X
5000X
500X
10kU X30 500um CHEM TECH
850X IMPACT
CRANIAL

(3)

CAUDAL



230X


X1500
4
CANDIDA
Mag :x30
Acc.V :10kV
Signal :SEI
WD :10mm
Spot size :40
Pressure :
:0.67mm
File Name :
W:***\04_409_4_30X.tif
(OUT) LAYER TO EDGE!
1200X
X30 500µm
CHEM TECH
LAYER OF PUBLIN? w/ CELLS
CRACK NO PICTURE
750X
3,500X

PRL ARCHIVE TRANSFER SHEET

THE ATTACHED MATERIALS ARE TO BE ARCHIVED

The following information must be present on each folder in order to archive:

Study Number S1086

Title of Study NO releasing polymer to prevent thrombus formation using an Aortic Button Model

Miscellaneous list of all other materials, i.e., tapes, CD, photos:

Archive sample.

Date: [redacted]

Signature:

J:\Forms\Operations\PRL Archive Transfer Sheet
Initial: 10/15/2002